REMARKS

The Applicants have amended Claims 1 and 21, and added new Claims 49 and 50. The specific changes to the amended claims are shown above, wherein the insertions are underlined and the ~~deletions are stricken through~~. The Applicants respond below to rejections and objections raised by the Examiner in the Office Action of October 2, 2003.

I. Objection to Specification

The Examiner has objected to the Specification because three co-pending U.S. patent applications which are incorporated by reference at page 1 lines 10-21 are not identified by their relationship to the present application. This application does not claim priority to these applications in any way. They have been listed in the specification for informational purposes only for the benefit of the Patent Office to help ensure consistent and complete examination, and for the information of any future reader of this application after issuance.

For the Examiner's information, each of these applications is still pending. The issue fee has been paid in the 09/804,580 application, and an Office Action has been issued for the 09/804,458 application.

II. Rejections under 35 U.S.C. § 102 and 103

The Examiner has rejected Claims 1-21 under 35 U.S.C. §102, as allegedly being anticipated by Sinha *et al.* (1995). The Examiner has also rejected Claims 1-29 under 35 U.S.C. §103 as unpatentable over WO96/41166 Tsien et al, in combination with Jacobs (1997).

Independent Claims 1 and 21 have been amended to more clearly define the nature of the transmembrane potential change being induced by the electrical stimulation. Specifically, the term "controlled" has been deleted, and the transmembrane potential change is now described as arising from a series of two or more electric fields, and as "advancing predominantly in one direction away from a starting transmembrane potential over the course of said series of electric fields." This type of transmembrane potential change is demonstrated in the application in Figures 10 and 14 for example. As shown in these Figures, the transmembrane potential rises continuously over the course of a series of pulsed electric field applications covering several

seconds. This form of transmembrane potential change is not disclosed or suggested by any of the prior art of record.

Regarding the content of the prior art, the Examiner acknowledges that the Tsein WO96/41166 reference fails to disclose using electrical stimulation to modulate ion channel activity. For a teaching of electrical stimulation protocols, the Examiner relies on Sinha and Jacobs. Neither of these references describes or suggests the transmembrane potential change of the claims. In both Sinha and Jacobs, electrical stimulation is applied to CA1-CA3 hippocampal brain cells. In both of these references, the neural cell cultures undergo externally induced action potentials with each pulse stimulus. These action potentials do not produce a change in transmembrane potential that "changes predominantly in one direction away from a starting transmembrane potential over the course of said series of electric fields" as set forth in independent Claims 1 and 21.

When a neuron or muscle cell undergoes an action potential, the cell first depolarizes from about –70mV to much closer to 0 mV due to the activation of sodium channels in the membrane. Sodium channel activation produces sodium diffusion into the cell from the higher sodium concentration in the extracellular environment. After a few milliseconds, the sodium channels enter an inactivated non-conducting state, and potassium channels become activated. This results in a flow of potassium out of the cell from the higher potassium intracellular environment. This outflow of potassium lowers the transmembrane potential to a hyperpolarized state slightly more negative than –70 mV. This hyperpolarized state re-sets the sodium channels back to their resting state, and the cell potential then relaxes back to the normal transmembrane potential of about –70 mV, at which point the cell is ready to undergo another action potential cycle.

Because the sodium channels are voltage gated, they can be induced to open and initiate an action potential in response to an external electrical stimulus. These action potential cycles (which are not unidirectional, as they swing from –70 mV, up to near 0 mV, down to below –70 mV, and back to –70 mV) are only milliseconds in duration, and are produced in response to each individual one of the stimulation pulses of Sinha and Jacobs.

Figure 4B of Sinha, for example, shows the "action potential in the stimulated presynaptic fibers," where it can be seen that each spike in the VSD voltage dependent fluorescence signal is

bidirectional in potential change over a 20 millisecond period, and corresponds to action potential depolarization and repolarization in response to a single applied voltage pulse.

The Jacobs reference is similar in its teaching. In the bottom half of the second column of page 4130 of this reference, it states: "Most likely, each 1 msec field pulse induces a single action potential in this preparation." Jacobs never measures the transmembrane potential change induced by either a single pulse or a series of pulses, but instead measures a somatic calcium increase over a series of pulses.

Action potentials produce large swings of transmembrane potential in both positive and negative directions and are produced in response to individual pulse stimuli. They do not produce transmembrane potentials that change predominantly in one direction away from a starting transmembrane potential over the course of a series of applied electric fields. Sinha and Jacobs cannot be construed as teaching the transmembrane potential changes claimed in independent Claims 1 and 21. It is this unidirectional modulation of transmembrane potential over a series of pulses that makes the present invention much more useful in drug discovery than the induced action potentials of Sinha and Jacobs.

None of the remaining art of record cures this deficiency. It is respectfully requested that the outstanding rejections of Claims 1 and 21 be reconsidered and withdrawn.

The remaining claims, including new Claims 49 and 50, depend directly or indirectly from independent Claims 1 or 21 discussed above. With respect to the change to Claim 22, where the word "exogenously" is amended to read "endogenously," support for this change can be found specifically, for example, on page 55, lines 28-29 of the specification as filed. It is submitted that these claims are therefore allowable for at least the same reasons as set forth above with regard to the independent claims.

CONCLUSION

The Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims pursuant to the Examiner's rejections under §§ 102 and 103, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of these amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

Any claim amendments which are not specifically discussed in the above remarks are not made for patentability purposes, and it is respectfully submitted that the claims satisfy the statutory requirements for patentability without the entry of such amendments. These amendments have only been made to increase claim readability, to improve grammar, or to reduce the time and effort required of those in the art to clearly understand the scope of the claim language.

If the Examiner has any questions which may be answered by telephone, he is invited to call the undersigned directly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 1/30/04

By: _____

Thomas R. Arno
Registration No. 40,490
2040 Main Street, 14th Floor
Irvine, CA 92614
(619) 235-8550

S:\DOCS\ETA\ETA-1933.DOC
122903